

Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing.

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Circulation-derived cells play a crucial role in the healing processes of tissue. In early phases of tendon healing processes, circulation-derived cells temporarily exist in the wounded area to initiate the healing process and decrease in number with time. We assumed that a delay of time-dependent decrease in circulation-derived cells could improve the healing of tendons. In this study, we injected platelet-rich plasma (PRP) containing various kinds of growth factors into the wounded area of the patellar tendon, and compared the effects on activation of circulation-derived cells and enhancement of tendon healing with a control group (no PRP injection). To follow the circulation-derived cells, we used a green fluorescent protein (GFP) chimeric rat expressing GFP in the circulating cells and bone marrow cells. In the PRP group, the numbers of GFP-positive cells and heat-shock protein (HSP47; collagen-specific molecular chaperone)-positive cells were significantly higher than in the control group at 3 and 7 days after injury. At the same time, the immunoreactivity for types I and III collagen was higher in the PRP group than in the control group at early phase of tendon healing. These findings suggest that locally injected PRP is useful as an activator of circulation-derived cells for enhancement of the initial tendon healing process. J. Cell. Physiol. (c) 2008 Wiley-Liss, Inc.

Research, use of platelet-rich plasma continues to expand

Platelet-rich plasma (PRP)—a component of whole blood containing powerful, transforming growth factors—has garnered worldwide attention as a possible biologic method to treat tendinosis and tendon tears, as well as many other challenging conditions.

In Europe, PRP is being used to treat conditions ranging from tendinosis to osteitis pubis. This past November, I had the opportunity to take a European “PRP Tour”—to share my clinical work on PRP and to learn about and witness how European orthopaedists are using PRP to enhance healing. I was also invited to speak at several meetings focused on research and clinical experiences with PRP.

Achilles tendon repair in Sweden

Upon my arrival in Linköping, about two hours west of Stockholm by train, I met with Per Aspenberg, MD, PhD, the author of several articles on the successful use of PRP to enhance tendon healing. We discussed the number of researchers around the world who are investigating and assessing the value of PRP in orthopaedic surgery.

The next morning, I was asked if I would like to observe Dr. Aspenberg and his colleague, Torsten Schepull, MD, perform an Achilles tendon repair. I welcomed the opportunity. The nurses and operating room staff were very cordial and, fortunately for me, spoke excellent English.

As the patient was prepped for surgery, I was asked whether I would like to scrub in on the case. The patient was lightly sedated and in a prone position; a local anesthetic was injected around the incision site. After the surgery had started, I was informed that this patient was the first case in a prospective, randomized trial to measure the impact of receiving autologous PRP in an Achilles tendon repair.

The lead surgeon made the incision, expertly mobilizing the tendon edges. After checking the treatment allocation data on the computer, the surgeons found that this patient would receive PRP. Although the patient was awake, headphones prevented him from hearing any of the discussion, so he remained unaware of the randomization decision. To ensure the accuracy of the research, no further discussion on the use of PRP was permitted around this patient.

Just before the surgeon closed the tendon sheath, he embedded 0.8 mm tantalum balls into the tendon above and below the tear site. This allows for noninvasive analysis of tendon elongation at 6- to 10-week intervals postsurgery. Researchers will be able to calculate and compare tendon length among patients in the PRP group and those in the control group. I found this to be a particularly unique and novel method, which will provide information for the clinical trial and additional noninvasive biomechanical data on the differences between the two groups. The PRP was injected into and around the repaired tendon after the surgeon closed the tendon sheath.

Other uses for PRP

In the afternoon, orthopaedic surgeons from throughout northern and Eastern Europe attended a meeting to discuss their research and clinical experiences with PRP.

From his studies with rat models, Dr. Aspenberg demonstrated how PRP enhances Achilles tendon stiffness and force to failure. Taco Grosen, MD, from the Netherlands, presented preliminary data from his prospective, randomized trial of PRP versus cortisone for treating chronic tennis elbow.

Dr. Grosen demonstrated how PRP produces significantly better statistical outcomes than cortisone for pain relief and functional scoring at 6 months after a single injection. This is consistent with my findings in "Treatment of Chronic Elbow Tendinosis with Buffered Platelet-Rich Plasma," published in the *American Journal of Sports Medicine*.

Orthopaedic surgeons from Sweden, Finland, and Poland also made presentations on PRP. Ongoing investigations include the use of PRP in the treatment of partial tears of the anterior cruciate ligament (ACL), meniscal tears, and osteitis pubis.

Krzysztof Ficek, MD, from Poland, reported that he has some success using PRP with osteitis pubis—a notoriously difficult condition. Eight of nine patients treated with PRP are doing very well.

Italian Ministry of Health funds PRP study

At the Galeazzi Orthopedic Institute, in Milan, I met with Professor Gieseppe Banfi and Laura de Girolamo, MD, about their prospective study of tendinosis funded by the Italian Ministry of Health.

We discussed the confusion they routinely encounter in Italy about the growth factors in PRP. Some patients and Italian ministry administrators think growth factors are growth hormones. Part of their job is convincing patients and administrators that PRP is not a growth hormone!

Drs. Banfi and Girolamo provided the following statement about their study. "All the patients suffer from chronic osteoarticular pathology and are exposed to a nonsteroidal anti-inflammatory drug (NSAID) therapy. They will undergo either anterior cruciate ligament reconstruction surgery with PRP or Achilles/patellar tendon surgery with PRP and will be clinically evaluated for 12 months according to a predetermined protocol.

"A biopsy of the patient's cartilage tissue will be evaluated by other centers during an in-vitro study culturing the patient's chondrocytes with their PRP. The aim of the in-vitro study is to evaluate a number of inflammatory markers and molecular 'targets' implicated in the inflammatory and healing response of the cartilage taken from patients exposed to NSAID and to the PRP treatment, which in the future might be used for diagnostic and therapeutic purposes."

The investigators have asked me to evaluate their protocol and to contribute to their study.

Genoa: PRP and the treatment of tendinopathy

In Italy, I also attended the 15th annual meeting of the Ligurian Arthroscopy Association organized by Ferdinando Priano, MD. I had been asked to give two lectures—one on the basic science of PRP and the other on my own clinical experiences with it.

With more than 300 orthopaedic surgeons, basic scientists, and hematologists in attendance, the meeting focused on the potential use of PRP in the treatment of tendinopathy.

Dr. Priano shared his experience using hyaluronic acid for tendon-related disorders. Piero Volpi, MD, presented the results of a study using ultrasonic guided injections of PRP for patellar tendinosis. Pietro Randelli, MD, showed an excellent video of his technique using PRP to augment arthroscopic rotator cuff repairs.

Conclusion

My week in Europe showed me that interest in PRP as a treatment to enhance healing has grown quite dramatically, with speculation about using this technology for cartilage, ligament, and even disk pathology. Significantly more basic science and clinical investigations, however, will be required to fully validate the use of PRP.

I plan to continue these interactions with my esteemed European colleagues via the Internet and in person at future meetings. I have been honored to be part of the PRP discussions in both the United States and Europe. I recently learned that orthopaedic surgeons in Brazil, Australia, and Hong Kong have also used PRP in orthopaedic surgery. I look forward to hearing the results from my orthopaedic colleagues throughout the world.

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How does PRP work?

Platelet-rich plasma (PRP) contains powerful growth factors, including transforming growth factor-beta (TGF- β) and vascular endothelial growth factor (VEGF). PRP has been shown to enhance the proliferation and migration of a variety of cell types including tenocytes and mesenchymal stem cells. This in-vitro data helps explain why PRP may be helpful for patients with chronic tendinosis. Published studies also note that PRP has a strong stimulant effect on capillary regeneration. This improved vascularity may be another way PRP improves overall tendon health.

Not all PRP is the same. PRP that has not been activated by thrombin or calcium may be the preferred form. The collagen within tendons can be expected to activate the platelets slowly, resulting in a sustained release of growth factors. PRP activated by thrombin and or calcium, however, results in rapid discharge of growth factors, which may not be ideal.

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